REMARKS

Interview Summary

The Office action mailed 29 May 2008 included an examiner's interview summary for the personal interview held on 13 December 2007. The summary is substantially correct. However, applicant notes one misstatement concerning the disclosure of the reference discussed at the interview. U.S. Patent No. 6,183,744 at cols. 1-2 provides a general discussion of CLL and, separately, a general discussion of the use of CD20 antibodies for treating B-cell lymphomas. The '744 patent indicates that the observed efficacy of a CD22 antibody was unexpected in view of a report that chronic lymphocytic leukemias do not generally express CD22 (not CD20). As explained at the interview, the present application teaches that, as was known in the art, CD20 is expressed at relatively low levels on CLL cells. *See* specification at paragraph 0130.

Outstanding rejections

All of pending claims 29-97 are rejected under 35 U.S.C. § 103 over three separately stated combinations of references:

- The November, 1997, package insert for RITUXAN® (rituximab) (referred to as "IDEC Pharmaceuticals Corp." in the Office action) as taken in view of Kaminski (U.S. Patent No. 5,843,398), Lerner (U.S. Patent Application Publication No. 2003/ 0018014), and Stenbygaard (*Breast Cancer Res. Treatment*, 1993)
- McLaughlin (*J. Clin. Oncol.*, 1998) as taken in view of Kaminski '398, Kaminski (U.S. Patent No. 6,090,365), Lerner '014, and Stenbygaard
- Anderson (U.S. Patent No. 5,736,137) as taken in view of Kaminski '398, Kaminski '365, and Stenbygaard

The teachings of the three primary references (The RITUXAN® package insert, McLaughlin, and Anderson) serve comparable functions in each of the rejections, as do the collective teachings of the remaining references. Accordingly, it is efficient to treat the rejections in a single discussion.

The Kaminski '398 and '365 patents claim priority to the same original filings and are based on the same disclosure. Because the specifications of the patents are substantially identical, where the discussion below cites Kaminski '365 the relevant arguments apply equally to Kaminski '398.

With this reply, applicant provides the declaration under 37 C.F.R. § 1.132 of David P. Schenkein, M.D ("SD"). Dr. Schenkein trained as a clinical oncologist and was treating cancer patients, including CLL patients, at the time of the present invention. SD ¶¶ 2-3. He is therefore qualified to speak to the understanding of a person of ordinary skill in the art in the field of the invention in the relevant timeframe.

The primary references describe the use of rituximab to treat non-Hodgkin's lymphoma

RITUXAN® (rituximab), a therapeutic CD20 antibody, was first approved by the Food and Drug Administration (FDA) in 1997 for the treatment of patients with relapsed or refractory low grade or follicular, CD20 positive, B cell non-Hodgkin's lymphoma (NHL). The RITUXAN® package insert (PI) reflects this approval. SD ¶ 6. The document does not refer to the treatment of CLL.

McLaughlin describes results of the phase III clinical trial that supported the approval for commercial marketing of RITUXAN® reflected in the RITUXAN® PI. SD ¶ 7. Notably, the trial described in the reference *specifically excluded* CLL patients (*i.e.*, those having high counts of circulating lymphocytes). SD ¶ 8. This reference certainly would not have steered a person of ordinary skill toward using rituximab to treat CLL.

Anderson describes phase I/II clinical trials using rituximab (termed C2B8 in the patent) for treatment of histologically confirmed B-cell lymphoma. SD ¶ 9. There is no mention of CLL in the Anderson disclosure, and nothing that would suggest to a person of ordinary skill that the NHL data it describes would correlate with therapies for CLL. *Id.*

None of the additional references suggests using a CD20 antibody to treat CLL

The examiner states that Kaminski "teaches the administration of a CD20 antibody for the treatment of B cell [CLL]." Office action, page 4. But in fact, although the Kaminski disclosure includes some discussion of CLL and some possible treatments for it, *none* of the methods described by Kaminski that make use of a CD20 antibody involve treating CLL patients. As Dr. Schenkein explains, the Kaminski disclosure focuses on the use of CD20

antibodies to treat non-Hodgkin's lymphoma, not chronic lymphocytic leukemia. SD ¶¶ 10, 12.

Moreover, the methods described by Kaminski involve the use of a therapeutic radiolabeled antibody. SD ¶ 11. Kaminski emphasizes the benefits of using such an antibody in view of the "limited efficacy of unmodified antibodies." *See* Kaminski '365, col. 2, lines 22-24; SD ¶ 11. The methods advocated by Kaminski are categorically excluded by independent claims 29, 55, and 97, and multiply dependent claim 95.

Neither the passages of the Kaminski patent that the Office cites, nor any other passages of the Kaminski patent, in fact describe the use of any CD20 antibody to treat CLL patients. *See* Kaminski '398 at col. 6, lines 6-14; col. 8, lines 9-16; Table 1; cited in the Office action at pages 4, 6, and 8.

The paragraph at col. 6, lines 10-18 of the '365 patent (corresponding to col. 6, lines 6-14 of the '398 patent) conveys the possibility that antibodies *other than* CD20 antibodies to treat a variety of B-cell malignancies other than lymphoma, including ALL, CLL, hairy cell leukemia, and chronic myeloblastic leukemia. SD ¶ 13. Dr. Schenkein explains that even as to these antibodies (*i.e.*, antibodies against CD21, CD22, CD19, or CD10/CALLA), the cited passage does not provide sufficient information to inform an oncologist which antibody should be tested for treating which type of cancer. This passage would not have informed a person of ordinary skill that CLL (or any of the other three categories of cancer it mentions) should be treated with a CD20 antibody.

The paragraph at col. 8, lines 12-47 of the '365 patent (including the passage corresponding to col. 8, lines 9-16 of the '398 patent) discusses the cell types that express CD20, noting that CLL cells, among others, express CD20. However, this passage does not indicate whether there is any possible clinical significance associated with this observation. Dr. Schenkein concludes that this paragraph simply characterizes the biology of CD20, and would not have suggested any therapeutic strategy to a person of ordinary skill in the art. SD ¶ 14.

Table 1 of the patents, noted by the examiner, reports the results of clinical experiments in ten patients with B-cell lymphomas. No results involving CLL patients are reported.

The dose ranges proposed by Kaminski at col. 10, lines 62-64 and col. 29, lines 47-56, noted by the Office at page 7 of the Office action, relate to treatments involving radioimmunotherapy of B-cell lymphoma. Neither of these passages mentions any treatment for CLL.

The dose of unlabeled B1 (a CD20 antibody) exemplified at col. 29, lines 47-52, 2.5 mg/kg, corresponds to about 96.2 mg/m^2 for an "average" 70 kg, 67-inch human. This dose is unambiguously outside the doses and dose ranges specified in claims 33, 34, 59, 60, and the claims that depend from them. The broader range of 0.2 to 40 mg/kg noted at col. 10, lines 62-64 of Kaminski '365, corresponds to a dose range of about 7.69 to 1,540 mg/m^2. The breadth of this dose range is so broad as to encompass a very large number of possible distinct doses, and is thus evidence of the nonobviousness of the doses and dose ranges specified in claims 33, 34, 59, 60. *See* M.P.E.P. § 2144.05.

The other teachings of the Kaminski patents noted by the Office simply do not relate to the use of a CD20 antibody to treat CLL. Instead, they relate to conventional chemotherapy. Similarly, Lerner '014 and Stenbygaard are not relevant to immunotherapy of CLL. SD ¶ 15.

CLL and NHL are different diseases

A person of ordinary skill in the art would not have found the description in the prior art of treatments for NHL highly relevant for understanding what kinds of treatments might be tried, let alone effective for CLL. *See* SD ¶ 17. To understand why this is so, it is important to appreciate that clinicians consider NHL and CLL to be decidedly distinct diseases.

The two diseases differ fundamentally on several levels. CLL tumor cells and NHL tumor cells exhibit characteristic phenotypic features that reflect their different cellular origins. SD ¶ 19. Importantly, among these differences is a reduced level of CD20 expression on CLL tumor cells, relative to NHL tumor cells. SD ¶ 20. These malignancies are also characterized by distinct cellular physiology, which in turn leads to differential sensitivity to various therapeutic agents. SD ¶ 21.

The clinical characteristics of the diseases are also dissimilar, and they affect different patient populations. SD ¶¶ 22, 23. Researches have defined disease

characteristics that allow clinicians to reliably differentiate between CLL and other diseases with certain characteristics in common. Among the more prominent distinctions is the much higher tumor burden that is one of the defining characteristics of CLL. SD ¶ 22.

Clinicians at the time of the invention approached NHL and CLL with different treatment plans and different expectations for therapy. The most effective treatment options for CLL are not those that are most effective for NHL. SD ¶ 24. The clinical management of the diseases, as well as the typical progression and outcome, also differ. SD ¶¶ 25-27.

Because of the differences in cell biology, clinical characteristics, and responsiveness to different therapies, a person of ordinary skill would not have found prior clinical experience for the treatment of lymphoma – either using rituximab as described in the RITUXAN® PI, McLaughlin, and Anderson, or using radiolabeled B1, as described in Kaminski – as a proper basis for concluding that the claimed methods of treating CLL are obvious.

The references do not demonstrate a reasonable expectation of success for practicing the claimed invention

For a reasonable expectation of success, the Office refers to "teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized." Office action at pages 4-5, 7, and 9. However, the fact that dosages of effective agents must typically be optimized does not establish a reasonable expectation of success for using a particular agent to treat a given disease if nothing in the prior art or the experience of the practitioner of ordinary skill would suggest that the agent will be effective for that disease.

The Office also indicates that a reasonable expectation of success would be established by the knowledge in the art that CD20 is expressed on tumor cells in 95% of patients having CLL. Office action at pages 5, 7, and 9. Dr. Schenkein explains, however, why a person of ordinary skill in the art would not consider this fact sufficient to support an expectation that CLL could be treated effectively using a CD20-directed therapy. SD ¶¶ 28, 29, 31.

Dr. Schenkein notes two factors that would have caused a clinical oncologist to consider that the knowledge of treating NHL with CD20 antibodies would not reasonably be

predictive of obtaining similar therapeutic benefit from the use of the same antibodies to treat CLL.

First, as was known at the time of the invention, CD20 is expressed at relatively low levels on CLL tumor cells, as compared to the levels present on NHL tumor cells. The lower level of antigen expression would have led to uncertainty whether CD20 antibodies could bind to CLL tumor cells at sufficient density to achieve a therapeutically beneficial inhibition or killing of the tumor cells. SD ¶ 29. A person of ordinary skill would have read the cited references with this uncertainty in mind. In particular, having knowledge of the low level of CD20 expression on CLL tumor cells, the person of ordinary skill would not have considered the fact that CD20 is expressed on 95% of CLL tumor cells, as Kaminski notes, as suggesting or predicting effectiveness for a CD20-targeted treatment for CLL.

Second, as was also known in the art, CLL is characterized by a high number of circulating tumor cells in the blood. The person of ordinary skill would have expected that the large number of tumor cells would create a "sink" of CD20 antibody-binding sites that would act to decrease the concentration of antibodies in circulation. The effect of such a decrease on the potential therapeutic efficacy of the antibody would not have been predictable. SD ¶ 30.

Dr. Schenkein states his belief that the combination of low density of CD20 molecules expressed on CLL tumor cells and the high numbers of tumor cells in circulation would have magnified the unpredictability concerning the potential of CD20 antibodies to treat CLL effectively. SD ¶ 31. In view of this evidence, it is clear that the common knowledge and experience of persons of ordinary skill in the art at the time of the invention would not have led to a reasonable expectation of success in practicing a method of treating CLL according to the present invention.

The pending claims are patentable over the cited references

The Office has not stated a *prima facie* case of obviousness. As Dr. Schenkein's declaration demonstrates, none of the cited references teaches or suggests using any CD20 antibody to treat CLL. Moreover, nothing in the prior art, or in the common experience of oncologists at the time of the invention, establishes a reasonable expectation of success for treating CLL using CD20 antibodies.

The cited references do not steer the skilled person in 1998 towards treating CLL with a CD20 antibody. Indeed, McLaughlin, the one reference that discusses CLL patients in the context of an immunotherapeutic trial protocol, teaches that CLL patients, defined as those having high numbers of circulating lymphocytes, were specifically *excluded* from the trial. In view of the unpredictability that would be expected from the higher tumor burden in CLL patients, the references teach away from extrapolating from treatments for NHL to new treatments for CLL. Accordingly, the present rejections should be withdrawn.

Conclusion

For the reasons set forth above, applicant requests that the examiner reconsider and withdraw all of the outstanding rejections under § 103.

Applicant believes that the application is in condition for allowance. Should the examiner have any remaining questions or concerns, she is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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